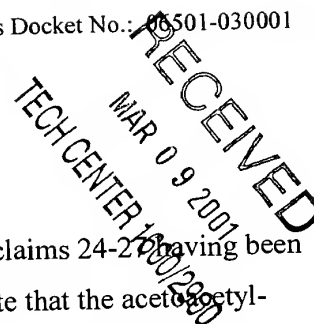


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#### REMARKS

Claims 7-14 and 23 are now pending in the present application, claims 24-27 having been cancelled by the above amendments. Claim 7 has been amended to recite that the acetoacetyl-CoA reductase contains the amino acid sequence of a naturally occurring Type II reductase, a limitation supported, for example, at page 4, last full sentence, of the specification. In addition, claim 7 now incorporates the limitation of claim 24, now cancelled. The significant differences between the four different types of reductase enzymes are described at pages 3-4, bridging paragraph, of the specification. Dependent claim 10 has been narrowed by deleting genera of reductases that encompass non-naturally occurring amino acid sequences. No new matter has been added by the above amendments.

In the last response, applicant added new claims, including claims 25-27. The Examiner has now withdrawn from consideration claims 25-27 as been drawn to an independent or distinct invention. To facilitate prosecution, applicants have cancelled claims 25-27.

Claims 7-10, 12, 14, and 23 are rejected under 35 U.S.C. § 112, first paragraph, for a failure of the specification to provide adequate enablement or written description support for the full scope of the claims. Applicant has now limited claim 7, the only pending independent claim, to acetoacetyl-CoA reductases that contain the amino acid sequence of a naturally occurring Type II enzyme. Since, in the last response, applicant has pointed out that naturally occurring reductases and genes encoding them are known to one skilled in the art who has read the specification, it is submitted that the claims are now commensurate with the support provided. Accordingly, the rejection should be withdrawn.

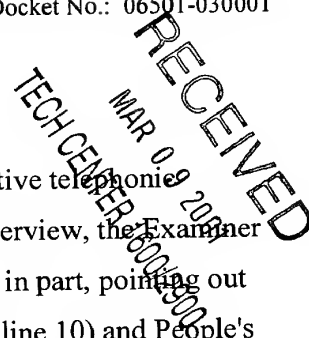
Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, for recitation of the allegedly indefinite term "stringent conditions." Applicant has deleted the portion of claim 10 that includes this term, rendering the rejection moot.

Claims 7-10, 14, 23, and 24 are rejected under 35 U.S.C. § 103(a) as obvious over Matsuyama et al. (U.S. Patent No. 5,559,030) in view of Peoples et al. (U.S. Patent No. 5,229,279) or Summerville et al. (WO 93/02187). Peoples and Summerville are cited by the Examiner to show that cloned acetoacetyl-CoA reductases are known and have been used in the reaction for which the enzyme is named, as exemplified in Peoples' Fig. 1. In that sense, Peoples and Summerville are cumulative references.

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Applicant thanks the Examiner and his Supervisor for the constructive telephone interview conducted with the undersigned on January 30, 2001. In that interview, the Examiner and Supervisor supported the single outstanding obviousness rejection by, in part, pointing out the similarities of the chemical structure of Matsuyama's substrate (col. 2, line 10) and Peoples' substrate for acetoacetyl-CoA reductase (Fig. 1). Applicant indicated that there were significant structural differences between the two, and the motivation to, e.g., include a halogen on Peoples' substrate was completely lacking. Applicant also pointed out that, although acetoacetyl-CoA reductase has been isolated at least since 1977 (see col. 1, lines 65-67, of Peoples) and the benefits of producing (S)-4-halo-3-hydroxybutyric acid ester have been known at least since the early 1980's (see page 1, first paragraph of BACKGROUND OF THE INVENTION of the specification), no one other than applicant has realized that a known enzyme (acetoacetyl-CoA reductase) can be used to facilitate a known commercially valuable chemical reaction. This is surely strong indicia of nonobviousness and shows that some structural similarity between Matsuyama's substrate and Peoples' substrate is insufficient to motivate the skilled artisan to use acetoacetyl-CoA reductase in the reaction recited in claim 7. Consequently, the Examiner's and Supervisor's contention that motivation to combine the references can arise merely from substrate similarities in Matsuyama and Peoples appears to be hindsight reconstruction. Applicant respectfully asks the Examiner to cast his mind back to the time the present invention was made and ask whether it would have been obvious to achieve the invention, particularly in light of the above discussion.

Applicant reserves the right to present broad claims reciting any acetoacetyl-CoA reductase that includes the amino acid sequence of a naturally occurring acetoacetyl-CoA in a continuation application. It is submitted that such claims are nonobvious. Nevertheless, in the interest of expediting prosecution, applicant has amended claim 7 to require that the naturally occurring acetoacetyl-CoA is a Type II enzyme.

Matsuyama tested the ability of selected microorganisms to produce optically active ethyl 4-chloro-3-hydroxybutyrate (cols. 8-9, Tables 1-4). Based on this testing, Matsuyama selected particular microorganisms that were especially useful in optically active conversion of the substrate. For example, a fungi of the genus *Kluyveromyces*, whose acetoacetyl-CoA reductase is a Type IB enzyme, is favored (see Table 1 and claim 1). In contrast, *Escherichia coli*, whose

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acetoacetyl-CoA reductase is a Type II enzyme, was not favored (Table 1). See pages 3-4, bridging paragraph, of the specification for organisms associated with the different types of enzymes. Thus, it appears that Matsuyama would teach away from using an organism harboring a Type II enzyme as required in claim 7, and at the very least Matsuyama clearly fails to provide any motivation to use a microorganism that contains a Type II enzyme. Indeed, as discussed in the present and previous responses, applicant can find no motivation at all in Matsuyama or elsewhere to use any acetoacetyl-CoA reductase in the reaction recited in claim 7. Accordingly, the rejection should be withdrawn.

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2-28-01

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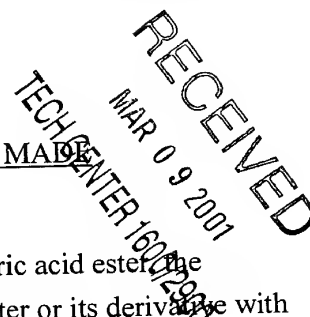
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

7. (Amended) A method for producing (S)-4-halo-3-hydroxybutyric acid ester, the method comprising asymmetrically reducing a 4-halo-acetoacetic acid ester or its derivative with a purified acetoacetyl-CoA reductase that can participate in a poly- $\beta$ -hydroxy fatty acid biosynthesis system, the purified acetoacetyl-CoA reductase comprising the amino acid sequence of a naturally occurring Type II acetoacetyl-CoA reductase.

10. (Amended) The method of claim 7, wherein said acetoacetyl-CoA reductase [is selected from the group consisting of:

- (a) a protein comprising] comprises the amino acid sequence of SEQ ID NO:9[;
- (b) a protein (1) comprising a modified amino acid sequence of SEQ ID NO: 9 in which one or more amino acid residues are added, deleted, or substituted and (2) capable of asymmetrically reducing 4-haloacetoacetic acid ester or its derivatives to produce (S)-4-halo-3-hydroxybutyric acid ester; and
- (c) a protein (1) encoded by DNA that hybridizes under stringent conditions to DNA consisting of SEQ ID NO: 10 and (2) capable of asymmetrically reducing 4-haloacetoacetic acid ester or its derivatives to produce (S)-4-halo-3-hydroxybutyric acid ester].